Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance and heart rate

J. F. Golding[1] & J. R. R. Stott[2]

[1]*Division of Psychology, University of Westminster, London, and* [2]*Centre for Human Sciences (DERA), Farnborough, UK*

Aims Hyoscine (scopolamine), which is effective in the prophylaxis of motion sickness, shows similar binding affinities to all of the five known muscarinic receptor sub-types. The effectiveness of hyoscine was compared with zamifenacin (UK-76654), which binds selectively to the muscarinic M_3 and m5 receptors.

Methods Eighteen subjects received hyoscine hydrobromide 0.6 mg, zamifenacin 20 mg, or placebo (double-blind cross-over design). Sessions were 1 week apart and the drug (oral) was given 90 min prior to a motion sickness test. Motion sickness was elicited by cross-coupled stimulation on a turntable. The rotational velocity was incremented by $2^\circ\,s^{-1}$ every 30 s, and a sequence (seq) of eight head movements of 45° was completed every 30 s. Motion tolerance was assessed as the number of sequences of head movement required to achieve moderate nausea. Pulse rate was recorded before and at 1 and 2 h after drug administration. Skin conductance activity in the frequency band 0.005–0.48 Hz, an index of sweat gland activity, was measured using Ag/AgCl electrodes on the palmar surfaces of fingers and across the forehead.

Results Both zamifenacin and hyoscine produced an increase in tolerance to the motion challenge ($P<0.01$) with no significant difference between the two drugs (5.0 ± 1.6 *vs* 5.7 ± 1.6 seqs. respectively, mean ± s.e.mean). Compared with placebo or zamifenacin, pulse rate fell following hyoscine administration (9 beats min^{-1}, $P<0.01$). Skin conductance was reduced following hyoscine compared with zamifenacin or placebo ($P<0.001$).

Conclusions These results suggest that compounds with selective M_3 and/or m5 antagonism possess activity against motion sickness. Antagonism at these receptors may be the basis of the anti-motion sickness action of hyoscine.

Keywords: hyoscine, muscarinic receptors M_3 m5, motion sickness, coriolis, heart rate, skin conductance

Introduction

The beneficial effect of hyoscine (scopolamine) in the prophylaxis of motion sickness is well established [1]. This drug shows similar binding affinities for all of the five known muscarinic receptor subtypes [2]. Zamifenacin (UK-76654), a selective muscarinic antagonist, has affinity for the M_3 muscarinic receptor subtype equivalent to that of atropine, while at the M_1 and M_2 receptors its affinity is less by factors of 50 and 100 respectively. The M_5 receptor has not been characterised pharmacologically, but studies using cloned receptors (m1—m5) indicate that zamifenacin also shows a high affinity for the m5 receptor (Wallis, personal communication).

We have compared the effectiveness of hyoscine and zamifenacin against motion sickness induced by cross-coupled motion. In addition the effects on heart rate, and on sweating measured by skin conductance, were investigated.

Correspondence: Dr J.F. Golding, Division of Psychology, University of Westminster, 309 Regent Street, London W1R 8AL, UK

Methods

Design

After a practice session without medication, each subject ingested hyoscine hydrobromide 0.6 mg, zamifenacin 20 mg, or placebo according to a double-blind three period cross-over design. Drugs were administered in the morning, followed at 90 min by the motion challenge. All sessions were at least 1 week apart. The dose of hyoscine hydrobromide 0.6 mg is the standard single dose for anti-motion sickness action. The choice of a 20 mg dose of zamifenacin was determined on the basis that doses 2 to 3 times greater than this can produce side effects typical of non-selective antimuscarinics (unpublished data on file).

Subjects

Subjects were eighteen healthy male volunteers aged between 19 and 46 years (mean age 28.7 s.d. 7.8 years) with intact vestibular function and not currently on other medications. The Motion Sickness Susceptibility Questionnaire (MSSQ) [3] mean percentile score was 52.7% (s.d. 31.5%) indicating

that the subject sample was only marginally more susceptible than the general population. The subjects were fully briefed, gave informed consent in writing and were free to withdraw at any time. The study received ethical committee approval from the Ethics Committee of the RAF Institute of Aviation Medicine.

Motion challenge

Cross-coupled (Coriolis) motion was employed to elicit motion sickness [4]. Subjects were blindfolded and seated on a turntable equipped with slip-rings for power and data lines. A staircase profile of (clockwise) rotational velocity was employed with increments from 2 to 120° s^{-1} in steps of 2° s^{-1} every half minute. Subjects performed a series of head movements to the left, right, back and forward in a random order according to tape-recorded instructions. Eight head movements of approximately 45° to head stops were completed every 30 s. Motion was stopped at moderate nausea (a sickness rating = 7, see below) or 35 min (70 head movement sequences), whichever was the sooner.

Motion sickness ratings and symptoms

Subjects rated their degree of motion sickness every 30s on the following seven point scale: 1 = no symptoms; 2 = any symptoms however slight; 3 = mild symptoms, eg, stomach awareness but no nausea; 4 = mild nausea; 5 = mild to moderate nausea; 6 = moderate nausea but can continue; 7 = moderate nausea, wish to stop motion challenge [5]. Following the cessation of the motion challenge, subjects remained seated and their recovery was recorded on the 1–7 sickness rating scale every 0.5 min from 1 to 5 min.

In the first minute of recovery a motion sickness symptom checklist was administered for: dizziness, bodily warmth, headache, sweating, stomach awareness, increased salivation, nausea, pallor, any other symptom(s). Symptoms were rated as nil = 0, mild = 1, moderate = 2, severe = 3.

Skin conductance

Skin conductance was recorded from 1st and 2nd finger palmar sites of the non-dominant hand, and from the left and right sides of the forehead close to the hairline approximately 2 to 4 cm above the eyebrows [6]. Ag/AgCl electrodes were attached with double-sided self-adhesive stickers (SLE Ltd). Total effective skin contact area was 0.32 cm^2 for each pair of electrodes. The electrolyte gel used was 0.05M NaCl in low substitution methyl cellulose gel (BDH Ltd). The concentration of NaCl was in the range found in human sweat [7, 8]. Skin conductance was measured using a constant current (10 μA) mains-isolated device. This device presented the output in two forms: the d.c.-coupled (tonic) skin conductance level (SCL) and the amplified 0.14 Hz high pass filtered (phasic) skin conductance response (SCR). These signals were anti-alias filtered at 2Hz, digitised at a sampling rate of 5 Hz (A/D 12 bit), displayed on-line and stored on optical disc.

Heart rate

Pulse rate was measured at the wrist over a 1 min period, after sitting at rest for approx 5 min. The pulse rate was recorded immediately prior to drug ingestion, at 1 h post-drug and at 10 min following the cessation of the motion challenge (approximately 2 h post-drug).

Drug side-effects checklist

A checklist was administered immediately prior to drug ingestion, at 1 h post-drug, and at 10 min after the cessation of the motion challenge (approximately 2 h post-drug). The requested symptoms were: drowsiness, dry mouth, blurred vision, headache, nausea, abdominal pain, dizziness, sweating, light-headedness, and any other symptoms (all symptoms scored nil = 0, 1 = mild, 2 = moderate, 3 = severe).

Other measures

In the 30 min period from 1 to 1.5 h post-drug, measurements were made of the vestibulo-ocular response to 0.1 Hz angular oscillation, visual pursuit at frequencies of 0.15, 0.24, 0.37 and 0.85 Hz, each at ±4° s^{-1} peak velocity and voluntary saccadic eye movements to targets displaced by 5, 10, 15 and 20 deg to left and right [9, 10], and short term memory performance using the Sternberg Memory Test [11].

Statistical analysis

Data were analysed by ANOVA for run order (order of the treatment sessions), treatment (placebo, zamifenacin, hyoscine), and time to endpoint. ANOVAs revealed no run order (session) effects on any variable and for brevity these are not detailed below in results. Effects were further isolated by Newman-Keuls tests. Since some subjects on some treatment sessions reached the maximum cut-off time of 35 min, the data were treated as being right censored and maximum likelihood estimations were made for the right censored values with appropriate adjustments of degrees of freedom. For the analysis of the SC data, a 2 min block of SC data was extracted from the beginning of the motion challenge, i.e. well prior to the onset of initial symptoms of motion sickness in all subjects, and a further block of SC data was taken over the 2 min preceding the endpoint of the motion challenge, i.e. during the period of time of maximum motion sickness. The differences between the first and last 2 min blocks of each finger and head skin conductance data set were addressed as a time factor in this analysis. The spectral powers for the first 96 frequencies of each block, representing the frequency band 0.005 to 0.480 Hz, were combined and log transformed to normalise the variance of the data set. In addition, the 5 min period following the cessation of the motion challenge, referred to as the 'recovery phase', was analysed in 1 min blocks.

Results

Tolerance to the motion challenge

The number of sequences of head movements required to produce each sickness rating level is shown in Figure 1.

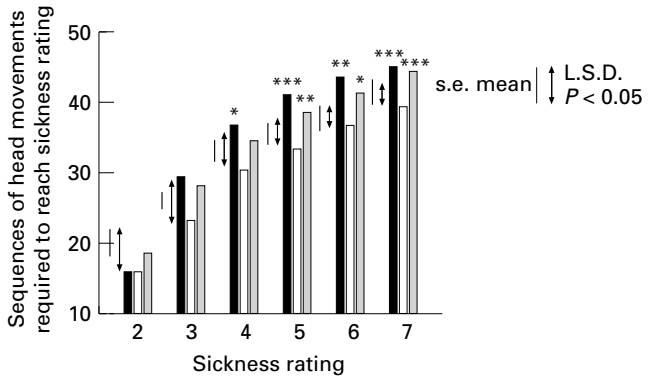

Figure 1 The mean number of sequences of head movements required to produce each motion sickness rating is plotted for the three treatments. Tolerance to the motion challenge was significantly greater following hyoscine (■, 0.6 mg) or zamifenacin (▦, 20 mg), taken 90 min prior to the motion challenge, as compared with placebo (□). Motion sickness was elicited by cross-coupled stimulation on a turntable. The rotational velocity was incremented by 2 deg.s^{-1} every 30 s, and a sequence of eight head movements of 45 deg was completed every 30 s. The sickness rating varied from 1 = no symptoms to 7 = moderate nausea and wish to stop. (L.S.D. least significant difference). ⋆$P<0.05$, ⋆⋆$P<0.01$, ⋆⋆⋆$P<0.001$ drug *vs* placebo.

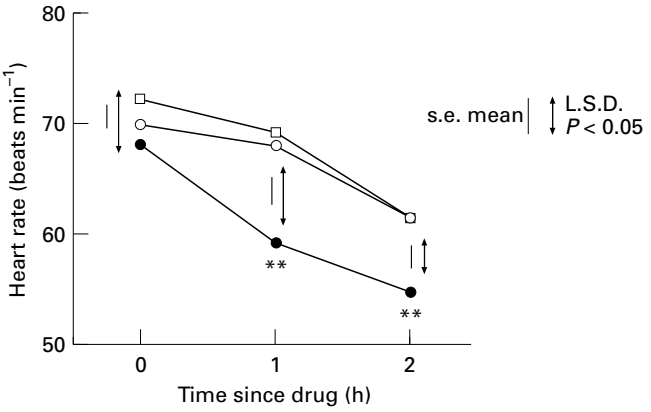

Figure 2 The mean heart rate at 0 h (immediately prior to drug ingestion), 1 h and 2 h is plotted for the three treatment conditions. The motion sickness challenge began at 1.5 h. The 2 h is an approximate time, being 10 min after the end of the motion sickness challenge. Heart rate was significantly lower following hyoscine (●, 0.6 mg) but not zamifenacin(□, 20 mg), as compared with placebo (○). (L.S.D. least significant difference). ⋆⋆$P<0.01$ drug *vs* placebo.

Both zamifenacin and hyoscine treated subjects showed an increase in tolerance to the motion challenge compared with placebo ($P<0.01$). Hyoscine treatment showed a difference from placebo of 5.7 ± 1.6 seqs (mean ± standard error of comparison), and zamifenacin a difference of 5.0 ± 1.6 seqs. Differences between zamifenacin and hyoscine at endpoint or at other sickness rating stages were non-significant. ANOVA of sequences to each sickness rating showed no significant treatment effect at sickness rating = 2, a marginal effect ($F=2.9$, df 2,23, $P=0.05$) at sickness rating = 3, and significant treatment effects ($P<0.01$) at all higher sickness ratings.

Recovery of sickness ratings after motion endpoint

Sickness ratings reduced rapidly after cessation of motion; most subjects had recovered to the level of slight symptoms by 5 min. There were no significant differences between treatments over all time points or at any particular time point.

Symptom scores at motion endpoint

Only sweating ($F=8.3$, df 2,24, $P<0.01$) and bodily warmth ($F=3.2$, df 2,24, $P=0.05$ marginal) showed treatment effects. With hyoscine, sweating scores were lower than those for placebo ($P<0.01$) or zamifenacin ($P<0.05$). The zamifenacin sweating score was lower than that for placebo but not significantly so. Bodily warmth scores were lower for hyoscine than for placebo ($P<0.05$). All other comparisons were not significant.

Drug side-effects checklist

The majority of positive responses were in the 'mild' category. At 2 h post-drug, i.e. after the motion challenge, the incidence of reponses increased in many of the categories irrespective of treatment condition. The only item to show a significant overall treatment effect was dry mouth ($F=4.8$, df 2,24, $P<0.05$), where the mean scores for hyoscine and zamifenacin were both significantly higher than those for placebo ($P<0.05$).

Heart rate

Figure 2 presents the mean heart rate data. ANOVA showed a strong time effect ($F=33.2$, df 2,24, $P<0.001$), a strong treatment effect ($F=7.4$, df 2,24, $P<0.01$) and significant treatment x time interaction ($F=4.3$, df 4,47, $P<0.01$). The source of the significant time effect was the significant fall in mean heart rate from pre-drug to 1 h post-drug ($P<0.01$), followed by a further significant drop in heart rate from 1 h to 2 h post-drug ($P<0.001$). The source of the significant treatment and treatment x time effects was that, whereas there were no significant differences between treatments pre-drug, at 1 h and 2 h post-drug lower mean heart rates (of the order of 9 beats min^{-1} overall) were observed with hyoscine compared with either placebo or zamifenacin ($P<0.01$).

Skin conductance

An example of skin conductance recording is shown in Figure 3. Mean skin conductance activity is presented in Figure 4, for the initial 2 min sample pre-motion sickness, and the final 2 min sample during motion sickness.

Forehead SC, expressed as μmho RMS in the frequency band 0.005–0.48 Hz, between the first and last 2 min of the motion challenge increased overall from 0.006 to 0.023 (time effect: $F=20.1$, df 1,12, $P<0.001$). A significant treatment effect was observed ($F=5.4$, df 2,24, $P<0.05$) at the forehead recording site, and a significant treatment x time interaction ($F=5.3$, df 2,24, $P<0.05$). The source of these effects was that while at the beginning of the motion

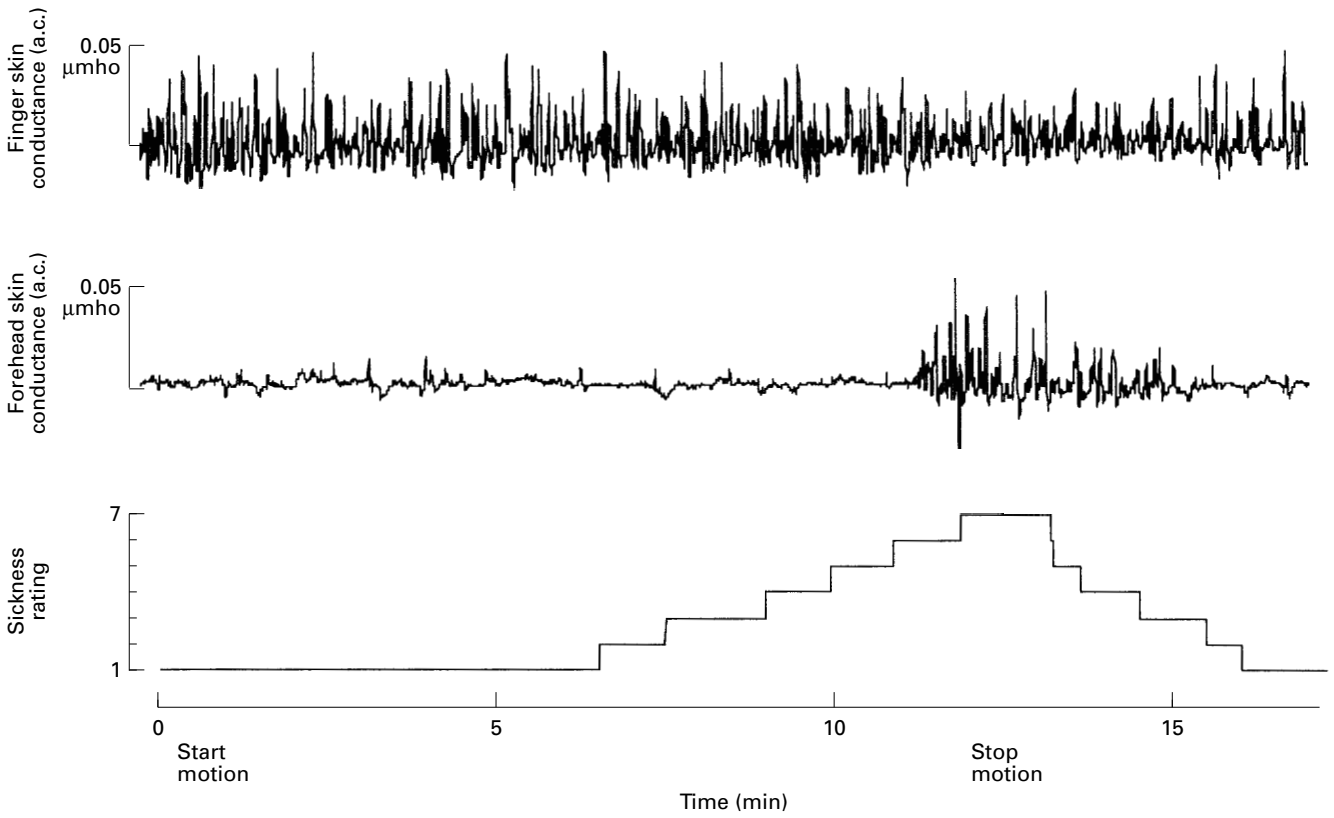

Figure 3 Example phasic skin conductance recordings at forehead and finger palmar recording sites from one subject during the motion challenge under placebo treatment. The simultaneously recorded sickness rating on the 1–7 scale is also shown. Note that, whereas the finger palmar site is active throughout reflecting nonspecific arousal responses to stimuli such as tape recorded instructions, the forehead site is quiescent until the onset of moderate nausea at around 12 min.

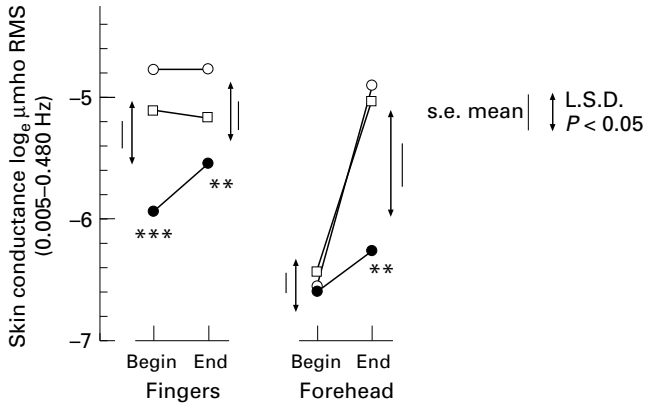

Figure 4 Mean phasic skin conductance activity based on 2 min samples from the beginning (no motion sickness) and end (during motion sickness) of the motion challenge, for the palmar finger and the forehead recording sites, by treatment condition placebo. (L.S.D. least significant difference). $^{**}P<0.01$, $^{***}P<0.001$ drug *vs* placebo. (● hyoscine 0.6 mg, □ zamifenacin 20 mg, ○ placebo).

challenge there were no significant differences between treatments, the SC at motion endpoint was lower following hyoscine than after either zamifenacin or placebo (0.0074 *vs* 0.025 or 0.028 μmho RMS, respectively, $P<0.01$).

Finger SC showed no significant time effect (first *vs* last 2 min of the motion challenge). The treatment effect for finger SC was highly significant ($F=11.7$, df 2,24, $P<0.001$) and the treatment x time interaction was not significant. The source of this effect was the reduction ($P<0.001$) of SC following hyoscine by an overall factor of 2.6 ± 1.2. Although SC was reduced following zamifenacin, the change was not significant compared with that after placebo.

For the forehead recovery phase SC, significant effects were observed for time ($F=9.9$, df 4,48, $P<0.001$), treatment ($F=5.5$, df 2,24, $P<0.05$), and time × treatment interaction ($F=3.4$, df 8,96, $P<0.01$). These effects were due to the significantly lower SC for hyoscine compared with placebo or zamifenacin ($P<0.05$). The SC for placebo and zamifenacin had declined to that for hyoscine by the 5th min. For the finger recovery phase SC, a highly significant effect was observed for treatment ($F=12.9$, df 2,24, $P<0.001$), but there were no significant time or time x treatment interaction effects. The source of the significant treatment effect was the lower finger SC observed with hyoscine compared with placebo ($P<0.001$) or zamifenacin ($P<0.01$). In addition, zamifenacin produced significantly lower finger SC than that after placebo ($P<0.05$).

Other measures

Vestibular-ocular, saccadic and Sternberg memory measures showed no significant treatment effects. Only the 0.37 Hz visual pursuit gain showed a significant treatment effect ($F=6.2$, df 2,23, $P<0.01$). This was due to the lower pursuit gain at this frequency with hyoscine as compared with placebo ($P<0.05$).

Discussion

The primary aim of this study was to investigate whether zamifenacin (UK-76654), which binds selectively to the M_3 and m5 receptors, was effective against motion sickness. At the dose used, zamifenacin demonstrated significant protective action against provocative motion, and the degree of protection was equivalent to that afforded by hyoscine. Lucot *et al.* [12] concluded from studies using selective muscarinic antagonists such as idaverine, that it was unlikely that M_1 and M_2 receptors were involved in motion sickness. He suggested that the M_3 subtype might be critical, and that '...if this suggestion is verified, then selective blockade of M_3 sites would prevent motion sickness while producing far fewer side effects than antimuscarinics in current clinical use.' The results of this study would seem to give weight to Lucot's speculation, although it must be noted that a role for the m5 receptor is equally possible, and the role of the m4 receptor in this context is as yet unknown.

A significant reduction in heart rate was observed with hyoscine, but not with zamifenacin. Reductions in heart rate by antimuscarinics such as atropine or hyoscine are thought to be due to blockade of M_1 receptors on postganglionic parasympathetic neurones, whereas larger doses can cause tachycardia by blocking vagal effects on M_2 receptors on the SA nodal pacemaker [13]. The lack of effect of zamifenacin on heart rate is thus explicable by virtue of its relative selectivity for muscarinic receptors other than M_1 or M_2.

The final (postganglionic) innervation of the sweat gland is muscarinic, explaining the reduction in skin conductance activity (SC) following hyoscine. Since the muscarinic postganglionic innervation of the sweat gland is thought to be of the M_3 type [14] zamifenacin might also have been expected to produce a significant reduction in skin conductance activity by virtue of its actions at such receptors. It is possible that the dose of zamifenacin was insufficient to produce consistent reductions in SC, although sufficient to produce increased tolerance to the motion challenge equivalent to that produced by hyoscine.

No severe side-effects were observed with either hyoscine or zamifenacin. Only one performance measure was significantly impaired, that of visual pursuit gain by hyoscine, zamifenacin showing no significant effect. With regard to subjective symptoms as elicited by the side-effects checklist, only dry mouth showed a significant treatment effect, with both hyoscine and zamifenacin showing a small but significant increase in subjective reports of dry mouth compared with placebo. Subjective sweating at the end of the motion challenge was significantly lower with hyoscine as compared with placebo, zamifenacin being without significant effect. Such effects as subjective dry mouth and reduced subjective sweating are consistent with the well-known profile action of antimuscarinics on secretory glands.

We conclude that compounds with selective M_3 and/or m5 antagonism possess activity against motion sickness. It is possible that antagonism at one or both of these receptors is the basis of the anti-motion sickness action of hyoscine.

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